Fundamentals of Management of the Hypertensive Patient

Edward D. Freis, M.D.

Senior Medical Investigator, Veterans Administration Hospital, Washington, D.C.

ABSTRACT

The diagnostic workup in hypertension seeks to identify the few curable forms of the disorder, to indicate those patients who are at increased risk of complications, and to reveal those complications that may already have occurred. Treatment is based on moderate sodium restriction and step-care therapy with antihypertensive agents. The cornerstone of drug therapy is a thiazide diuretic. Other agents, such as methyldopa, are added as required to achieve adequate control of blood pressure with a minimum of patient inconvenience. Compliance with therapy is vital, and the establishment of a therapeutic partnership between physician and patient increases the chance of successful long-term treatment.

INTRODUCTION

The emphasis on the diagnostic workup of the newly diagnosed hypertensive patient has changed in recent years. In the past, the workup was extensive and costly, with the purpose of determining whether the patient had a curable form of hypertension, such as pheochromocytoma or primary aldosteronism. However, the number of surgical procedures performed even at such a referral center as the Mayo Clinic[1] makes it clear that these curable forms of hypertension are extremely rare, accounting for perhaps only 1% of the hypertension seen in patients over 40. In younger patients these forms are seen more often, but they are still quite unusual. Today, an elaborate investigation is justified only in the patient who has suggestive clinical evidence of a curable form of hypertension and who is under 40. It is important to realize that surgical treatment, especially in patients over 40, is not particularly successful. In renovascular hypertension, the most common kind of curable hypertension, surgery is generally reserved for patients under age 45, especially those who do not respond to medical therapy. Only medical treatment is ordinarily used in patients over 50.

The Veterans Administration Cooperative Study[2,3] and the Public Health Service Hospital Study[4] have demonstrated the value of effective antihypertensive drug therapy in preventing such complications as heart failure, renal failure, dissecting aortic aneurysm, and

progression of hypertension to a more severe stage.

Elsewhere, there is also suggestive, if not definitive, evidence that treatment may reduce the incidence of myocardial infarction and sudden death.[5,6]

DIAGNOSTIC WORKUP

The purpose of the diagnostic workup is to identify curable forms of hypertension and to indicate the severity of the disease and the extent of target organ damage. The workup has been summarized in a risk evaluation record.

Obtaining a true blood pressure reading from a patient usually requires taking at least three readings at separate visits, because the stress of an initial examination often causes falsely high readings. In patients who are nervous and anxious, it is sometimes desirable to have a member of the family record blood pressures at home for two weeks, in order to get a more representative picture of the patient's blood pressure.

History taking for curable forms of hypertension seeks patient complaints of explosive periodic headaches and pounding of the heart, which suggest pheochromocytoma. Sudden onset of severe hypertension or sudden worsening of mild hypertension suggests renovascular hypertension. The patient should also be asked whether he or she has experienced such complications as stroke, myocardial infarction, congestive heart failure, angina, dyspnea on mild exertion, or nocturia.

Clinical investigations include a chest X-ray, which is not essential but which may show possible pulmonary disease or an enlarged heart. However, an electrocardiogram is a better way of identifying left ventricular hypertrophy, which is seen with high voltage in the leads over the lateral part of the chest, accompanied by inversion or flattening of the T-waves or sagging of the ST-segments. During clinical examination, the patient's optic fundi should be inspected for hypertensive changes.

Laboratory workup should include a routine blood count and urinalysis, the latter of which may reveal urinary tract infection or other underlying renal diseases as shown by cellular or granular casts in the urine or albuminuria.

Blood chemistries should include the serum potassium level. A low level of serum potassium, if the patient is not taking a thiazide diuretic, may indicate primary aldosteronism. An initial serum potassium and other electrolyte determinations are also useful in evaluating the changes produced by diuretic therapy. Serum creatinine and serum urea nitrogen are helpful in identifying unsuspected renal failure and are also useful as baseline measurements if a rise is seen in either level during therapy. Pretreatment uric acid levels are also helpful, because gout is common in hypertensive patients. Also, thiazide diuretics may increase uric acid levels. Most patients with elevated serum uric acid levels never develop clinical gout, although frank gout may be precipitated in certain patients.

Fasting serum glucose should be measured, with a level of 120 mg or above indicating, to many physicians, the presence of diabetes. Cholesterol and triglyceride levels should also be determined. Hyperglycemia, hypercholesterolemia, and hypertriglyceridemia are known to further increase the

risk of myocardial infarction, which is already high in hypertensives because of the hypertension-accelerated atherosclerosis. Recent evidence suggests that the measurement of high density lipoproteins is a useful predictor of myocardial infarction, the risk of future myocardial infarction being inversely related to the serum concentration of high density lipoproteins.[7]

The routine measurement of plasma renin levels as part of the diagnostic investigation of the hypertensive patient is a somewhat controversial topic. It has long been known that high renin levels are associated with severe hypertension. Recently it has been suggested, but not proved, that renin levels are independent indicators of the severity of hypertension, separate from blood pressure, and that a patient with low renin levels will be protected from complications of hypertension. However, other investigators have been unable to confirm this relationship. Furthermore, renin levels may not be the most reliable of tests, particularly when they are not correlated with 24-hour urinary excretion of sodium. In general, plasma renin levels appear to have little value in evaluating prognosis.

It has also been suggested that low-renin hypertensives have high extracellular fluid volume and should respond to diuretics, whereas high-renin hypertensives should respond to drugs that inhibit secretion of renin. Research may reveal the merit of these hypotheses, but for the practicing physician the important point is that high blood pressure itself is damaging for the patient and should be controlled by whatever drug or combination of drugs is most effective. There is as yet no substitute for an adequate therapeutic trial.

Reduction of Risk Factors

Reducing the weight of obese patients is extremely important and may in itself lower blood pressure to normal. The difficulty lies in motivating the patient to lose weight and then maintain a normal weight.

Restriction of saturated fats and cholesterol may help to retard the development of atherosclerosis, although the evidence is not conclusive.

Salt restriction is also helpful. Most patients will not continue on a very low sodium diet, but they may be persuaded to avoid extremely salty foods and snack foods and not to oversalt their food when cooking or at the table.

Patients who smoke cigarettes are advised to stop because of the known link smoking has to coronary disease, for the risk of coronary disease is already above average in these patients.

Moderate exercise is encouraged for its general health benefits.

Level of Blood Pressure

The most important factor in determining a patient's prognosis is the level of blood pressure. A number of long-term studies, including the Framingham study and our VA studies, have shown the relationship between level of blood pressure and degree of risk. The Framingham study, for example, demonstrated that hypertensives develop seven times more brain infarctions than normotensives. The risk was proportional to the blood pressure through-

out its range, increasing 30% for each 10-mm increment in pressure.[8]

Other Factors

Several other factors increase the risk in hypertensive patients and should be evaluated before starting treatment.

Age is one factor. The younger the patient, the more likely that hypertension will progress and the shorter will be the life expectancy. Life insurance statistics indicate that the 20-year mortality rate for patients with a blood pressure of 150/100 is five times greater than normal in the age range of 30 to 39 and is twice normal in the age range of 50 to 59.[9]

Sex is another factor. Men do not tolerate high blood pressure as well as women do. Mortality rates for men are one and one half to two times higher than those for women.[10,11]

Race is yet another consideration. Hypertension is about twice as prevalent in the black population as in the white,[12] and it is more severe among blacks. Hypertensive heart disease is seen at rates three to seven times greater for blacks of a given age-sex group than for whites of the same age-sex group.[13] Indeed, the rate of complications of hypertension is at least double that seen in whites.

Presence of target organ damage at the time of diagnosis greatly increases the risk of further complications, as do hypercholesterolemia and a family history of hypertensive complications. Hypertension aggravates and accelerates atherosclerosis, particularly of the coronary and cerebral arteries. Hypercholesterolemia and, to a lesser extent, hypertriglyceridemia, diabetes mellitus, and cigarette smoking are also associated with atherosclerosis of the coronary arteries. When any or all of these factors are present in a patient with hypertension, the risk of myocardial infarction or sudden death is considerably increased.[14]

Therapeutic Decisions

Regardless of the cause of hypertension, complications result from the elevated blood pressure. The aim of therapy is to lower the blood pressure and keep it at normal or close to normal levels with a minimum of inconvenience to the patient. The simpler and more convenient the regimen, the more likely the patient will comply with it.

The Veterans Administration Cooperative Study Group on Antihypertensive Agents[2,3,15] showed conclusively that reduction of blood pressure with antihypertensive agents prevented many hypertensive complications such as hemorrhagic stroke, congestive heart failure, accelerated (malignant or premalignant) hypertension, renal deterioration, dissecting aortic aneurysm, and progression of hypertension from mild to moderate or from moderate to severe forms. The only major complication that did not appear to be prevented by treatment was myocardial infarction.

The relationship between the physician and the patient is especially important in successful treatment. If the physician is convinced of the importance of treatment and if the patient is aware of the physician's concern, then the patient is more likely to stay in treatment. Follow-up visits are an important opportunity for the physician to

reinforce the patient's awareness of the need for therapy and the success of the measures used. This can be done by reporting to the patient his lowered pressure, thereby indicating the success of treatment.

Step-care therapy is empiric but effective in almost all patients. A thiazide diuretic is the cornerstone of treatment. The choice of a particular agent depends on how conscientious the patient will be in complying with therapy.

Age is another consideration. In patients over 60, it is usually wise to begin with a smaller dose of a thiazide than that used in younger patients. Baroreceptor activity is related to the elasticity of the carotid artery, and if the walls are relatively stiff, as they often are in older people, then the baroreceptors may be sluggish in responding to postural changes causing orthostatic hypotension. This may result in episodes of dizziness and fainting when the patient arises from a sitting or lying position. In general, older people do not moderate their blood pressure as well as younger people do.

Initiating Therapy

In patients under the age of 60, I begin therapy with a diuretic. If hydrochlorothiazide is used, my initial dose is usually 25 mg twice daily. In patients over 60, I initiate therapy with 25 mg of hydrochlorothiazide once a day.

The patient returns in one week if the hypertension is fairly severe, in two weeks if the problem is less urgent. If the blood pressure is not controlled at this visit, I double the hydrochlorothiazide dosage, bringing it to 100 mg per day for the younger patients and to 50 mg per day for those over 60. In both younger and older patients, I prescribe the medication on a b.i.d. schedule. Ordinarily, these are the highest dosages I use, and they are effective in lowering blood pressure to the desired level in about half of all patients. In my experience, older patients tend to respond to smaller doses than younger patients, probably because of their impaired baroreceptor responses.

When the hydrochlorothiazide dose is increased, there may be a proportionate increase in dose-related side effects. In these cases, the diuretic must be reduced, and if necessary, a second-step agent can be added.

Hydrochlorothiazide is contraindicated in anuria and when there is hypersensitivity to it or to any other sulfonamide-derived drugs. It should be used with caution in severe renal disease. In patients with renal disease, thiazides may cause azotemia. Cumulative effects of the drug may develop in patients with impaired renal function. Thiazides should be used with caution in patients with impaired hepatic function or progressive liver disease, since minor alterations of fluid and electrolyte balance may precipitate hepatic coma.

SECOND-STEP AGENTS

For patients who do not respond sufficiently to a thiazide diuretic, the next step is adding a sympathetic inhibiting agent or a vasodilator to the antihypertensive regimen. One can choose a sympathetic inhibitor from among those that act centrally, such as clonidine or methyldopa; those that act peripherally to deplete sympathetic nerve

endings of catecholamines, such as hydralazine; those that affect only the alpha-adrenergic portion of the sympathetic nervous system, such as prazosin; and those that block only the beta-adrenergic portion, such as propranolol. The centrally acting agents, such as methyldopa, although affecting both alpha- and beta-adrenergic systems, do not usually produce orthostatic hypotension. The agents that affect the alpha portion, such as prazosin, are more likely to produce this side effect, and one must be quite careful during the initial treatment period with such agents.

Vasodilators may be suitable for older patients, in whom sympathetic inhibitors may induce symptoms of postural faintness, weakness, and fatigue. The increased cardiac output seen with some vasodilators may have a beneficial effect on the elderly patient's sense of well being, and if the drug is begun at a low dosage and increased gradually to the therapeutic level, there is seldom any problem of angina occurring. For the patient who has angina, of course, propranolol is probably the most suitable second-level agent.

Reserpine is an effective second-step agent for many patients. Of course, the physician should not prescribe it for patients with mental depression, and extreme caution should be used in treating patients with a history of mental depression. Electroshock therapy should not be given to patients while on reserpine, or for seven days after the discontinuance of the drug, because severe and even fatal reactions have been reported with minimal convulsive electroshock therapy.

I do not use reserpine in patients with active peptic ulcers or in those with ulcerative colitis. The most commonly seen side effect is nasal stuffiness. Impotence may occur but is reversible on stopping the drug. At the first sign of depression, the drug must be discontinued. Small doses may minimize side effects, and many patients can be controlled on as little as 0.1 mg of reserpine daily.

Methyldopa is a useful second-step agent in conjunction with a thiazide, and it need be taken only twice a day. In my experience, patients are less likely to comply with any regimen that requires taking pills more than twice a day. The thiazide-methyldopa combination is useful in that the thiazide diuretic, by reducing blood volume, makes the patient more responsive to the antihypertensive effect of methyldopa and offsets the sodium retention that may occur with long-term use of methyldopa.

When methyldopa is added to a thiazide regimen, the patient is started at 250 mg twice a day for a total daily dose of 500 mg. If the response is not sufficient, at the next visit the dose is raised to 500 mg twice a day, and increased in this manner until a satisfactory response is seen or the total daily dose is 2,000 mg. The side effects most often seen are sleepiness and dryness of the mouth, although these tend to lessen with continued treatment. Impotence is sometimes seen with methyldopa, but in my experience much less often than with reserpine.

I do not use methyldopa in patients with active hepatic disease, such as acute hepatitis and active cirrhosis. I

also withhold it from patients in whom previous methyldopa therapy has been associated with liver disorders.

The great majority, perhaps 95%, of patients can have their hypertension controlled with one or another of the combinations of thiazide plus a second-step agent. The appropriate combination depends on blood-pressure response and the occurrence of side effects. It is wiser to seek a two-drug regimen that is effective than to prescribe a three-drug regimen, because patient convenience is greater with a two-drug regimen, and because the number of side effects is likely to be less with a two-drug regimen than with a three-drug regimen. If the patient does not respond to a particular two-drug combination, such as a thiazide plus propranolol, it may be helpful to pick a second drug that is quite different, such as methyldopa.

If the patient has impaired renal function, it may be useful to substitute furosemide for the thiazide diuretic in order to achieve sufficient reduction in volume.

For the fraction of hypertensive patients who still do not respond, despite adequate diuresis and compliance, referral to a teaching center specializing in resistant hypertension is the alternative.

Combination Therapy

Combination therapy offers important advantages to both patient and physician. The most important benefit is that the convenience of combination therapy improves patient compliance with the antihypertensive regimen. Also, the cost of the medication may be lower. Of course, it is essential that the physician titrate the individual drugs first and then determine whether there is a convenient combination of the agents employed.

Management Problems

Patients with coexisting diseases such as diabetes, various cardiovascular problems, and renal disorders present some difficulties in management.

In the case of diabetes, physicians are sometimes reluctant to prescribe thiazides for fear of worsening the hyperglycemia. Thiazides may worsen glucose tolerance to some extent and may elevate blood sugar. However, in terms of preventing complications, it is probably more important to control the hypertension than to control the blood sugar. Therapy should aim to control the hypertension first, which is often difficult to accomplish without a diuretic. If the blood sugar rises somewhat, treatment can be directed towards that. Beta-adrenergic blocking agents, of course, should not be used in insulin-dependent diabetics because they may disguise the symptoms of insulin shock.

The patient with cerebral vascular disease, who may have some senile changes, with difficulty in remembering recent events and in locating himself in time and place, probably should be treated cautiously because the mental symptoms may be made worse. Propranolol should probably be avoided in these patients since they may already be suffering from the effects of decreased cardiac output. A thiazide in small doses plus a vasodilator such as hydralazine, if a second drug is needed, may

be the best of therapeutic choices.

In the patient who has had a stroke, the situation is similar. One does not want to decrease cardiac output, but such a patient may have severe hypertension that requires several agents for control. The patient who has had a subarachnoid hemorrhage should be investigated to determine whether he has a surgically correctable aneurysm, but of course his blood pressure should be controlled first.

Congestive heart failure is usually not seen in any patient who is receiving adequate antihypertensive therapy that includes a diuretic. If congestive heart failure appears, it suggests that the treatment is inadequate, either in terms of diuresis or in terms of blood pressure control. In the VA cooperative study, no patients under treatment for hypertension developed congestive heart failure. It was only seen in the control group.

For patients who have had congestive heart failure in the past, it is important to make sure they are receiving adequate amounts of a diuretic and that their renal function is not impaired. If it is, they should be given furosemide. Good control of blood pressure is essential to preventing a recurrence of the congestive heart failure.

In my opinion, patients who have had myocardial infarctions in the past three months probably should not receive propranolol or hydralazine because of the risk of precipitating heart failure. Patients whose myocardial infarcts occurred more than three months previously can probably be treated in the same way as any other hypertensives.

Patients who have second-degree or greater heart block should not be given propranolol and probably not reserpine either. Both drugs tend to depress heart rates even further.

In atrial fibrillation, it is very difficult to obtain a true blood pressure reading, but there are no contraindications to any of the drugs discussed.

In patients with angina, reducing the blood pressure often benefits the angina. A thiazide plus propranolol is usually effective therapy.

Beta-adrenergic blockers should not, of course, be used in patients with a history of asthma, and it may be wise to avoid their use in patients with chronic obstructive pulmonary disease, since there is often an asthmatic component present.

Patients with impaired kidney function are difficult to treat because they are so resistant to drugs. They do not respond sufficiently to thiazide diuretics possibly because their glomerular filtration rates are so low. I have found that thiazide diuretics lose their effectiveness when the glomerular filtration rate falls to about 30% of normal. The serum creatinine level is then usually in the range of 4 to 6. At this point one must prescribe furosemide, because this diuretic remains active in the presence of renal failure, although higher than usual doses may be required. The drug also does not decrease renal blood flow and glomerular filtration rate in the majority of cases. As the sodium is removed by the loop diuretics, blood volume and blood pressure fall, but there is a rise in the blood urea nitrogen (BUN) and creatinine. In my opinion, this reflects merely a hemodynamic change and does not indicate increased renal damage. The

BUN and creatinine usually return to near-pretreatment levels in a month or two despite continued treatment. Finally, if the patient does not respond to furosemide and the creatinine rises to the range of 10 to 15, it will be necessary to put the patient on hemodialysis.

Patients with impaired kidney function can rarely be controlled with a single drug. Besides a diuretic, a helpful second-step drug is methyldopa. Because it is excreted primarily by the kidney, it is not excreted as rapidly as normal in the patient with impaired kidney function. Therefore, when the blood pressure starts to respond, the dosage should be reduced somewhat because of this cumulative effect. In my experience, patients with renal failure respond better to methyldopa than to most second-step drugs now available.

CONCLUSIONS

Step-care therapy provides effective treatment of hypertension for most patients. A thiazide diuretic is the basis of therapy, and the addition of one or more agents, such as methyldopa, will almost always control those who do not respond to a diuretic alone. When the agents have been titrated to suit the patient's individual needs, it may be appropriate to employ a combination agent (if the doses match those of the available combinations) as both an economy and to improve compliance. Cooperation and interaction between physician and patient are essential for successful therapy.

REFERENCES

1. Tucker, R.M. and Labarthe, D.R. (1977): Frequency of surgical treatment for hypertension in adults at the Mayo Clinic from 1973 through 1975. *Mayo Clin. Proc. 52,* 549.
2. Veterans Administration Cooperative Study Group on Antihypertensive Agents (1967): Effects of treatment on morbidity in hypertension: Results in patients with diastolic blood pressures averaging 115 through 129 mmHg. *J. Am. Med. Assoc. 202,* 1028.
3. Veterans Administration Cooperative Study Group on Antihypertensive Agents (1970): Effects of treatment on morbidity in hypertension: II. Results in patients with diastolic blood pressures averaging 90 through 114 mmHg. *J. Am. Med. Assoc. 213,* 1143.
4. U.S. Public Health Service Hospitals Cooperative Study Group, Smith, W.M., Chairman (1977): Treatment of mild hypertension. Results of a 10-year intervention trial. *Circ. Res. 40 (Suppl. 1),* 98.
5. Ahlmark, G., Saetre, H. and Karsgren, M. (1974): Reduction of sudden deaths after myocardial infarction. *Lancet 2,* 1563.
6. Green, K.G. (1975): Improvement in

prognosis of myocardial infarction by long-term beta-adrenoreceptor blockade using practolol. *Br. Med. J. 3,* 735.

7. Gordon, T., Castelli, W.P., Hjortland, M.C., Kannel, W.B. and Dawber, T.R. (1977): High density lipoprotein as a protective factor against coronary heart disease. The Framingham Study. *Am. J. Med. 62,* 707–714.
8. Kannel, W.B., Dawber, T.R., Sorlie, P. and Wolf, P.A. (1976): Components of blood pressure and risk of atherothrombotic brain infarction: The Framingham Study. *Stroke 7,* 327.
9. *Build and Blood Pressure Study* (1959): Volume 1. Society of Actuaries, Chicago.
10. Sokolow, M. and Perloff, D. (1961): The prognosis of essential hypertension treated conservatively. *Circulation 23,* 697.
11. Bechgaard, P. (1946): Arterial hypertension: A follow-up study of one thousand hypertonics. *Acta Med. Scand. Suppl. 172,* 3.
12. United States Public Health Service (1966): Hypertension and hypertensive heart disease in adults: United States 1960–62. Series 11, Number 13. National Center for Health Statistics, Washington.
13. Stamler, J. (1975): Epidemiology of hypertension: Achievements and challenges. In: *Hypertension: A Practical Approach*, p. 30. Editor: M. Moser. Little, Brown & Co., Boston.
14. Truett, J., Cornfield, J. and Kannel, W.B. (1967): A multivariable analysis of the risk of coronary heart disease in Framingham. *J. Chronic Dis. 20,* 511.
15. Veterans Administration Cooperative Study Group on Antihypertensive Agents (1972): Effects of treatment on morbidity in hypertension: III. Influence of age, diastolic pressure, and prior cardiovascular disease; further analysis of side effects. *Circulation 45,* 991.